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Contents: Prescribing for children

Prescribing for children

Children form one of the largest groups of patients consulting general practitioners. It is estimated that every year about 18% of all GP consultations concern children less than 16 years of age.[1]

This *Bulletin* aims to provide a general awareness of the factors that should be considered when prescribing for children. Whilst the use of unlicensed and 'off-label' drugs is an important issue a full discussion is beyond the scope of this article. Specific prescribing information such as dosage, administration and formulation details are available from paediatric formularies or drug information centres (see **Information sources** on page 8).

Introduction

Children are continually changing with respect to growth, psychosocial development and pharmacodynamic response. The Royal College of Paediatrics and Child Health (RCPCH) suggests that when considering drug use, childhood is divided into the following age ranges:[2]

- **Neonate - birth to 1 month**. This covers the changes immediately after birth (infants under 37 weeks gestation require special consideration).
- **Infant - 1 month to 2 years**. This covers the early growth spurt.
- **Child - 2 to 12 years**. This covers the gradual growth period.
- **Adolescent - 12 to 18 years**. This covers the adolescent growth spurt to final height.

SUMMARY

* When considering drug use in children, the following age groups should be used: **neonate** (birth to 1 month), **infant** (1 month to 2 years), **child** (2 to 12 years) and **adolescent** (12 to 18 years).

* **Children are not 'mini-adults'**. Paediatric doses should be obtained from a paediatric dosage reference text and not extrapolated from the adult dose.

* The availability of a product in a suitable dosage form is not necessarily an indication of its suitability for children. Prescribers should consider the excipients in a preparation as they may cause adverse effects.

* Compliance in children is influenced by the formulation, taste, appearance and ease of administration of a preparation. Prescribed regimens should be tailored to the child's daily routine. Where possible, treatment goals should be set in collaboration with the child.

* The Medicines Act 1968 and European legislation make provision for doctors to use medicines in an 'off-label' capacity or to use unlicensed medicines. However, **individual prescribers are always responsible for ensuring that there is adequate information to support the quality, efficacy, safety and intended use of a drug before prescribing it.**

* Adverse drug reaction profiles in children may differ from those seen in adults. Doctors and pharmacists should report suspected adverse drug reactions to the Committee on Safety of Medicines (CSM), even if the product is being used in an 'off-label' manner or is an unlicensed product.

The RCPCH intend that these age ranges will be used as the standard reference ranges in the future to ensure consistency.[2]

Is a prescription necessary?

The fear of missing something serious and the perceived threat of illness are reported to strongly influence parental behaviour. This may be reflected in GP consultations for non-urgent conditions.[3]

The decision to issue a prescription should be based on clinical grounds. However, parents often interpret the issue of a prescription as an indication that the doctor has taken their concerns seriously. A study of parental attitudes to acute illness found that many parents assessed the need for antibiotics based on their beliefs of the illness severity rather than its cause. Anticipating this belief and discussing it with the parent may reduce the feeling of unmet needs if a prescription is not issued.[4]

The same study reported that parents felt excluded from the assessment process and were not reassured by the comment "it's just a virus". They felt this was too vague and often indicated that the doctor was unsure of the diagnosis.[4] These discrepancies between parental beliefs and clinicians' practices must be addressed if parents are to be seen as partners in their child's health care.

Inappropriate prescribing may lead to increased consultations. However, doctors should give appropriate advice which takes into account the concerns of parents.

Unlicensed and 'off-label' medicines

In order to ensure that medicines are safe, effective and of a suitable quality, they must have a product licence (now called a marketing authorisation) before being marketed in the UK. The product licence includes the indication, dose, route of administration and age group of patients for which the drug may be used.

Some medicines that are given to children are either:

- not licensed for use in children or are used outside the terms of their product licence (i.e. **'off-label'** use), or
- not licensed for any indication or age group (i.e. the drug is **unlicensed**).

Drugs may be unlicensed for a variety of reasons (see **table 1**). A recent study in five European countries reported that almost half of the drugs used in hospital paediatric wards were unlicensed or 'off-label'.[5] This is an area of concern, since it means that the risks or benefits of using these drugs have not been examined by the licensing authority.

Licensing arrangements constrain pharmaceutical companies but not prescribers. The Medicines Act 1968 and European legislation make provision for doctors to use medicines in an 'off-label' capacity or to use unlicensed medicines. Prescriptions for such therapies are often initiated in hospital, but GPs may be asked to continue prescribing. However, **individual prescribers are always responsible for ensuring that there is adequate information to support the quality, efficacy, safety and intended use of a drug before prescribing it.**

Some Health Authorities suggest that GPs should not prescribe unlicensed or 'off-label' drugs. However, it may be difficult to continue supply from distant hospitals. Other Health Authorities suggest that patients should be told if the drug is unlicensed or 'off-label' and even recommend that written consent is obtained before starting treatment.

Patients or parents should be given information on the use of an unlicensed or 'off-label' drug, otherwise the patient information leaflet may be confusing. Ideally, information specific to the situation should be provided. The Medicines Committee, a joint committee of the RCPCH and the Neonatal and Paediatric Pharmacists Group are providing general patient information leaflets explaining the need for unlicensed and 'off-label' drug use in children.

Interest in this subject has led to the publication of European Guidelines on the Clinical Investigation of Medicinal Products in Children.[6] These state that pharmaceutical companies and licensing authorities have a responsibility to ensure that children have timely access to safe and effective medicines, which have accurate, scientifically justified, prescribing information.

There is a need to improve the provision of paediatric information in the manufacturers' Summary of Product Characteristics (SPC). When first submitted for licensing, the amount of information on paediatric use may be limited or absent leading to statements such as, "*contra-indicated in children*" or, "*insufficient information to recommend use in children*". This can make it difficult for health professionals to make informed decisions on the risk:benefit of using a medicine for a particular indication, and even to identify whether it is licensed for use in children. A statement on unlicensed and 'off-label' drug use is found in *Medicines for Children* (see **Information sources**).

Drug handling

The various organs, body systems and enzymes that handle drugs, develop at different rates. Therefore, throughout childhood, the response to drugs varies. To ensure that children receive rational and effective drug therapy, an understanding of the factors affecting drug disposition is necessary (see **table 2**). These factors interact during treatment and should not be considered in isolation. Drug dosage and the

Table 1. Examples of why a drug in use may be unlicensed.

- It is only just undergoing clinical trials in adults.
- It has been imported from another country.
- It has been prepared extemporaneously.
- It has been prepared under a specials manufacturing licence.
- The product is not a medicine but is being used to treat a rare condition e.g. metabolic disease.

Oral Absorption

- ***Variable gastric and intestinal transit time***
  In young infants, gastric emptying time is prolonged and only approaches adult values at around 6 months of age. In older infants, intestinal hurry may occur.
- ***Increased gastric pH***
  Gastric acid output does not reach adult values until the second year of life.
- ***Other factors***
  Gastrointestinal contents, posture, disease states and therapeutic interventions, such as drug therapy, can also affect the absorption process.

Distribution

- ***Increased total body water***
  As a percentage of total body weight, the total body water and extracellular fluid volume decrease with increasing age. Neonates require higher doses of water soluble drugs on a mg/kg basis than adults.
- ***Decreased plasma protein binding***
  Plasma protein binding in neonates is reduced as a result of low levels of albumin and globulins and an altered binding capacity. High circulating bilirubin levels in neonates may displace drugs from albumin.

Metabolism

- ***Enzyme systems mature at different times*** and may be absent at birth, or present in considerably reduced amounts.
- ***Altered metabolic pathways*** may exist for some drugs.
- ***Metabolic rate increases*** dramatically in children and is often greater than in adults. Compared with adults, children may require more frequent dosing or higher doses on a mg/kg basis.

Excretion

- ***Complete maturation of renal function is not reached*** until 6-8 months of age.

Table 2. Factors affecting drug disposition in children.

choice of formulation are also influenced by the developmental changes in childhood.

What dosage should be used?

Children are not 'mini-adults'. Paediatric doses should be obtained from a paediatric dosage reference text and should not be extrapolated from the adult dose. *Medicines for Children* (see **Information sources**) includes prescribing guidelines and individual drug monographs. It contains information on licensed, unlicensed and 'off-label' uses of medicines in children. The RCPCH intend it to be a national formulary providing GPs with the information they need to prescribe such medicines in general practice or to share care.

Which preparation should be used?

The choice of drug and its formulation are influenced by several factors such as the intended route of administration, the child's age, availability of preparations, concomitant therapy and underlying disease.

The oral route is usually the most convenient and preferable. Liquid preparations may be necessary for younger children, although some may cope well with solid dosage forms. Parents are usually the best source of information on a child's capabilities. Where possible, to avoid dilution, oral syringes should be used for the administration of oral liquids.

Parents must be discouraged from adding medicines to an infant's feed. Interactions may occur with milk feeds in particular, and if the entire feed is not taken, a proportion of the dose will be lost. Parents should be told when it is not appropriate to crush a solid dosage form (e.g. modified-release preparations).

The rectal route of administration is not favoured in the UK. However, it can be a useful route for patients who are vomiting or who are reluctant or unable to take oral medication. Some drugs, such as theophylline, are erratically absorbed from the rectum and should never be given by this route. The rapid onset of action of other preparations is invaluable e.g. rectal diazepam solution stops seizures rapidly and can be easily given in an emergency.

Children lack the co-ordination required for the use of aerosol inhalers. Alternative devices, such as large volume spacers and masks, dry powder and breath activated devices have significantly improved the management of paediatric respiratory disease. Guidance on the most appropriate device for age can be found in paediatric formularies (see **Information sources**).

The availability of a product in a suitable dosage form is not an indication of its suitability for children. Some commercially available products contain excipients such as alcohol, propylene glycol or dyes, which may themselves cause adverse effects.

Sugar-free preparations should be used where available, to help prevent dental caries. A variety of alternative sweetening agents (e.g. aspartame, sorbitol and glycerol) are used in place of sucrose, but can cause problems in some patients. Sorbitol or glycerol may produce diarrhoea if large doses are given. Aspartame should be used cautiously in phenylketonuria because of the phenylalanine content. When products containing sucrose cannot be avoided, the teeth should be brushed after each dose.

Specially formulated products may be necessary in some cases. These may be formulated in a different strength to proprietary products. Good communication between primary and secondary care is required to avoid medication errors and to ensure continuity of supply.

Compliance

Since parents are often responsible for the administration of medicines to their children, the compliance of both parent and child must be considered. Although literature about noncompliance in children is limited, it is considered to be a widespread problem, similar to that reported in adults.[7]

Noncompliance may be caused by various factors such as resistance of the child to taking the medicine, complicated dosage regimens, misunderstanding of instructions and apparent ineffectiveness or side-effects of treatment. Different considerations are necessary for older children and adolescents who may be responsible for their own medicines. For example, they may be unwilling to use their medication due to peer pressure.

Several general principles should be considered in the approach to improve compliance. Attention should be given to the formulation, taste, appearance and ease of administration of treatment.

Compliance is usually better when fewer drugs are prescribed.[7] The regimen should be simple and tailored to the child's daily routine. In very young children, who tend to sleep a great deal and wake when hungry, it may not be possible to give the medicines as prescribed. It is preferable for doses to be scheduled for the child's waking day.

Many health professionals counsel the parents only, rather than involving the child in the counselling process. Where possible, treatment goals should be set in collaboration with the child.

Explicit instructions should be provided. As well as verbal counselling, parents often want written information. However, current patient information leaflets must reflect the SPC and so are often inappropriate. If a drug is used in an 'off-label' manner, statements such as "*not recommended for use in children*" may cause confusion and distress. Care needs to be taken to ensure that the information provided is appropriate for both the parents and the child.

Medicines in schools

Children with chronic conditions, such as asthma or epilepsy, and those receiving treatment (e.g. antibiotics) for an acute illness, may require medicines to be administered at school. In addition, medical emergencies may occur at school or on school trips which require prompt drug administration before the arrival of the emergency services. These may include anaphylaxis (associated with food allergy or insect stings), severe asthma attacks and fits.

Neither, the Department of Health nor, the Department of Education provide national guidelines that deal specifically with administration of medicines by teachers. Some Local Education Authorities produce local codes of practice. Where there are no guidelines, individual schools are left to determine their own policies.

Whenever possible, the use of products which avoid the need for administration during school hours should be considered (e.g. modified-release preparations or drugs with long half-lives). When administration at school is unavoidable, consideration should be given to prescribing and supplying the school time dose in a separate labelled container. Most schools will request written permission from parents to administer the medicine, or may ask parents to return to school to give the medicine themselves. This subject has been discussed in more detail elsewhere.[8,9]

When treating chronic conditions, prompt communication about changes to drug treatment between hospital doctors, GPs, parents and school staff are essential to avoid medication errors.

Adverse drug reactions (ADRs)

Many currently available drugs do not include information on their safe and effective use in children. Ethical issues have always placed a restraint on the evaluation of drugs in the paediatric population and studies conducted in children have tended to include only small numbers. Yet, ADR profiles in children may differ from those seen in adults and may not be predicted by studies in adults.

Doctors and pharmacists should report suspected ADRs to the Committee on Safety of Medicines (CSM) even if the product is being used in an 'off-label' manner or it is unlicensed. The CSM now has a subgroup on paediatric medicines.

Conclusion

When prescrbing for children, doctors must be familiar with the many factors which influence drug therapy. Paediatric reference texts can provide guidance on appropriate drug choice, dosage, formulation and administration. However, the individual prescriber is responsible for ensuring that adequate information exists to support the use of a specific drug.

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References

1 McCormick A, Fleming D, *et al.* Morbidity statistics from general practice: fourth national study, 1991-1992. London: HMSO, 1995
2 Licensing medicines for children. A report of the joint working party of the British Paediatric Association and the Association of the British Pharmaceutical Industry on the development of medicines for children. British Paediatric Association. London, 1996
3 Kai J. What worries parents when their preschool children are acutely ill, and why: a qualitative study. BMJ 1996; **313**: 983-986
4 Kai J. Parents' difficulties and information needs in coping with acute illness in preschool children: a qualitative study. BMJ 1996; **313**: 987-990
5 Conroy S, Choonara I, *et al.* Survey of unlicensed and off label drug use in paediatric wards in European countries. BMJ 2000; **320**: 79-82
6 European Agency for the Evaluation of Medicinal Products. Note for guidance on clinical investigation of medicinal products in children. 1997; CPMP/EWP/462/95
7 Matsui DM. Drug compliance in paediatrics: clinical and research issues. Pediatr Clin North Am 1997; **44**(1): 1-14
8 Bannon MJ, Ross EM. Administration of medicines in school: who is responsible? BMJ 1998; **316**: 1591-1593
9 Anon. Using medicines in school. Drug Ther Bull 1994; **32**: 81-83

Information sources

Medicines for Children
RCPCH Publications Ltd, London 1999.
This is a paediatric formulary. Other formularies also available from paediatric hospitals.

Drug information centres and local hospitals
See BNF for details of regional drug information centres.

DIAL (Drug Information Advisory Line) a national unit providing paediatric medicines information. **Tel:** 0151 252 5837 **E-mail:** info@dial.org.uk
Alder Hey, Royal Liverpool Children's NHS Trust, Dept. of Pharmacy, Liverpool.

The Royal College of Paediatrics and Child Health (RCPCH) www.rcpch.ac.uk

The Neonatal and Paediatric Pharmacists Group (NPPG) www.nppg.demon.co.uk

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